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Research Article

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Identification of Potential Adverse Events After COVID-19 mRNA Vaccines in Danish Children Using Healthcare Registries

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Abstract

Editor's Note: The following research article is an accepted manuscript awaiting peer review. Reviews of this article are forthcoming.

Background: COVID-19 vaccines have been administered to children worldwide. Investigating potential rare adverse events to the vaccine require post-marketing surveillance. Health registries can be useful tools.

Objective: We aimed to assess the potential for identifying self-reported rare adverse events in health registries.

Methods: A case-series was established via telephone interviews with parents of 21 Danish children aged 5-17, who had experienced new onset symptoms following Pfizer BNT162b2 vaccination, perceived by parents to be attributable to the vaccination. Participants were recruited via social media.

Results: All children had been vaccinated with Pfizer BNT162b2; 11 (52%) experienced new onset symptoms after dose 1 and 10 (47%) after dose 2. Nine (43%) had diagnoses that shared features of autoimmune illnesses; six (29%) had long-lasting infectious symptoms; 17 (81%) had an identifiable ICD-10 code.

Discussion and conclusion: The self-reported adverse events varied largely in their presentation; however, most were autoimmune or infectious. The present study does not establish any causal relations between COVID-19 vaccines and the observed diseases. The experienced diseases and symptoms can be difficult to identify in health registers, due to variation in their timing and diagnostic coding. It could be relevant to group rare diseases when conducting register studies.

Keywords: COVID-19, mRNA vaccine, autoimmunity, children, adverse events, non-specific effects.

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1. Introduction

More than half of the world's population has been immunized with at least one dose of SARS-CoV-2 (COVID-19) vaccine.[1] The most common administered vaccine types in European children and adolescents are messenger RNA (mRNA) vaccines, including Pfizer (Comirnaty, BNT162B2) and Moderna (Spikevax, mRNA-1273).[2] In Denmark, up to 80% of children aged 5-17 years received at least one dose and the vast majority were vaccinated with the Pfizer vaccine; only ~1000 children received Moderna.

The phase 3 mRNA trials enrolled a total of approximately 25,000 children aged 6 months to 17 years.[3] Few serious adverse events (SAEs) were observed.[4,5,6,7,8,9] Post-marketing follow-up detected an increased risk of post-vaccination myocarditis at a rate of about 1/3000 in adolescent males after the second dose of Pfizer.[10]

Rare adverse events can be particularly difficult to discover in phase 3 trials due to a limitation on study population sizes and duration of follow-up and may require post-marketing studies.[11,12] Such studies could be based on national health registers in countries like Denmark, with an extensive public funded health care system and well-documented registers, linking information on health care utilization, socio-economy, general demographics, etc., on an individual level via a personal identification number.[13,14,15,16]

In the present paper, we aimed to evaluate the challenges in identifying rare adverse events using health registry data.

We established a case-series by conducting interviews with parents of children experiencing new-onset disease following immunization with an mRNA COVID-19 vaccine and performed a descriptive analysis of the reported conditions, where we consider the timing and nature of these conditions including disease category based on the provided ICD-10 codes (if any).

We did not aim for representativeness of possible adverse events following vaccination but assessed a sample of experienced adverse events in children believed by their parents to be related to the mRNA COVID-19 vaccines. Also, we did not aim to establish causal links between COVID-19 vaccines and the reported adverse events as doing so based on individual cases is not possible.

2. Methods

The study was conducted in Denmark, where COVID-19 vaccines to children were

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introduced in May 2021 for the 16-19-year-olds, July 2021 for the 12-15-year-olds, and in November 2021 for the 5-11-year-olds. From July 2022, COVID-19 vaccines have not been offered to children under 18 years of age Denmark without a physician's prescription.

The aim of the study did not require a representative sample of those with self-reported adverse events. Participants were recruited through social media posts on Facebook, LinkedIn, and Twitter. Inclusion criteria were as follows: **1)** The child had received the implicated vaccination prior to turning 18 years of age, **2)** The child had experienced onset of new symptoms following receipt of a COVID-19 vaccine, and **3)** The parent/guardian attributed the new symptom(s) to the vaccination.

Telephone interviews were conducted between March and June 2023. The list of questions is shown in the Supplementary Material. Questions included time of vaccination, time of positive COVID-tests (if such had been performed), the symptoms experienced by the child after receiving COVID-19 vaccine, how long post-vaccination and how long post-positive COVID-19 test (if applicable) these symptoms occurred. Specifically, regarding contact with the healthcare system, parents were asked about healthcare/hospital visits, ICD-10 diagnosis assigned at hospital encounters (if any) and whether they had reported the symptoms/disease to the Danish Medicines Agency and/or the Danish Patient Compensation.

In Denmark, all patients examined in a hospital setting are registered in the Danish National Health Registers, including the ICD-10 diagnoses related to the contact on an individual level.[15] Diagnoses from General practitioners (GPs) and private practicing medical specialists are currently not available for research from the national registers. For the present study, data on medical history was provided by the parents, and not obtained via the national registers.

In addition to the interviews, we conducted a post-hoc literature search, including post-marketing surveillance studies and reports, reviews and case reports to investigate if any of the reported diseases had been described as possibly associated with the vaccines, and what the level of evidence for this was. This search was done using PubMed and included studies in English published from January 2020 to March 2025.

3. Ethics

The study was approved by the Regional Legal Services (SDU RIO, notification number 11.883) and the Research Ethics Committee (SDU REC, approval ID 23/19402). Written informed consent was obtained from the participants to publish this paper.

4. Results

A total of 25 people contacted us for study participation, and 21 children and adolescents were included. Two children were excluded (one with mild fever on the day of vaccination as only symptom, and one who was not vaccinated but had symptoms of Long-COVID), and two adults with post-vaccination symptoms were excluded due to the age restrictions.

Table 1 presents characteristics: 14 (67%) were female, the median age at first COVID-19 vaccine was 13 years (range 6 to 17 years). All children had received the Pfizer vaccine. Seven (33%) had documented prior or simultaneous positive PCR test for COVID-19 by the time of either COVID-19 vaccination. The table also outlines visits to GPs, private practicing medical specialists, and hospital departments related to the experienced symptoms along with previous vaccination history and baseline health information.

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Table 1. Baseline characteristics of each included participant.

ID	Sex	Age in years at first COVID-19 vaccine	COVID-19 vaccines 1st and 2nd	Positive COVID-19 PCR test	Received recommended childhood vaccines	Health conditions prior to COVID-19 vaccination	Consulted General practitioner	Consulted Private specialist [a]	Hospital admission
1	Male	6	October 2021 January 2022	October 2021	Yes	None	Yes	No	Yes
2	Male	8	January 2022 -	December 2021	Yes	None	Yes	No	Yes
3	Male	9	December 2021 January 2022	February 2022	Yes	None	Yes	No	No
4	Male	9	March 2022 April 2022	April 2022	Yes	None	Yes	No	No
5	Female	10	December 2021 December 2021	Yes, before vaccine (date unknown)	Yes	Allergy, asthma	Yes	No	No
6	Female	10	January 2022 January 2022	January 2022	Yes (except HPV[b])	None	Yes	Yes	Yes
7	Female	11	August 2021 September 2021	No known infection	Yes	None	Yes	No	Yes
8	Female	11	December 2021 January 2022	February 2023	Yes	None	Yes	Yes	Yes
9	Female	12	December 2021 December 2021	January 2022	Yes	None	Yes	No	Yes
10	Male	12	December 2021 December 2021	January 2022	Yes	None	Yes	No	Yes
11	Female	13	January 2022 -	No known infection	Yes	None	Yes	No	Yes
12	Male	13	December 2021 December 2021	No known infection	Yes	None	Yes	No	Yes
13	Female	13	November 2021 December 2021	November 2020, February 2022	Yes	One Rolandic epilepsy attack at age 8, mild learning difficulties.	Yes	No	Yes
14	Female	13	July 2021 August 2021	February 2023	Yes	Migraine	Yes	No	Yes
15	Female	14	May 2021 May 2021	September 2022	Yes (except HPV[b])	None	Yes	No	Yes
16	Female	14	August 2021 -	January 2022	Yes	None	Yes	No	Yes
17	Female	14	August 2021 September 2021	August 2022	Yes (except 2nd HPV[b])	Healthy, low IgM resolved	Yes	Yes	Yes
18	Female	14	November 2021 December 2021	July 2022	Yes	None	Yes	Yes	Yes
19	Female	15	August 2021 August 2021	February 2022	Yes	None	Yes	Yes	Yes
20	Male	15	December 2021 December 2021	March 2020	Yes	None	No	No	No
21	Female	17	June 2021 July 2021	January 2022	Yes	None	Yes	No	Yes

[a] Children registered as having consulted a private specialist all attended the same ME/CSF clinic.

[b] Human Papillomavirus vaccine

Prior to being vaccinated with an mRNA COVID-19 vaccine, all children had received all recommended childhood vaccines according to the Danish Childhood Vaccination Program,[17] with the exception of three children not receiving all the vaccines against human papillomavirus (HPV) recommended at age 12. No adverse events from any of the previously administered vaccines were reported by parents. 17 children (81%) had no known underlying health conditions prior to being vaccinated. Participant 5 had pre-existing asthma and allergy, participant 13 had one previous Rolandic epilepsy attack, participant 14 had migraines, and participant 17 had prior history of low immunoglobulin M level, now resolved.

A summary of occurrence and nature of the experienced symptoms after COVID-19 vaccination, along with a presentation of the provided ICD-10 diagnoses, is presented in **Table 2**.

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Table 2. A short description of each participant's medical history following COVID-19 vaccination

ID	COVID-19 vaccine-associated medical history	Symptoms after first dose	Symptoms after second dose	Identifiable ICD-10 code	Other ICD-10 diagnoses not identifiable*	Timing of symptom onset post-vaccination
1	After 2nd COVID-19 vaccine immediate development of fever, nausea, headache, vomiting. Symptoms were present for approximately ten days, then disappeared for two weeks, hereafter again present for one or two weeks. These cycles with and without symptoms has lasted for more than one year. Hospitalized, with low white blood cells count and low platelets.	None	Yes (fever, nausea, headache, vomiting)	DD696 Thrombocytopenia, unspecified	-	Immediate
2	Increasingly tired for weeks after 1st (and only) COVID-19 vaccination. From January 2022 school absence, fatigue, headache, nausea. Lost energy to even speak. Admitted to a pediatric department, no sign of neuro-infection. Admitted at a socio-pediatric department for 14 days during autumn 2022, suspected autism. No further psychiatric evaluation, but has drastically improved since early 2023, language returned but still very tired.	Yes (fatigue, headache, nausea)	NA	DG933 Post viral fatigue syndrome	-	Near immediate
3	Received 1st COVID-19 vaccine without adverse reactions. A few hours after 2nd vaccine development of fever and rhinitis. Symptoms have been present almost non-stop since vaccination. Very high frequency of school absence since debuting these symptoms. Seen the GP a few times. No hospital contacts.	None	Yes (fever, rhinitis)	-	-	Within a few hours
4	Received 1st COVID-19 vaccine without adverse reactions. Two months after 2nd vaccine a severe Herpes Simplex outbreak. Have since then had fever and sinusitis almost every week. Constant headaches. Seen the GP a few times. No hospital contacts.	None	Yes (Herpes Simplex, fever, sinusitis, headache)		-	After two months
5	Had COVID-19 infection prior to being vaccinated. Received both COVID-19 vaccine without immediate adverse reactions. In the weeks after 2nd vaccine development of joint and muscle pain. Pre-existing allergy and asthma worsening. Sudden angioedema a year after the vaccines, unknown cause, seen GP, no hospital admission.	None	Yes (joint and muscle pain, allergy and asthma worsening)	-	-	Within weeks
6	Fatigue and nausea immediately after vaccination in January 2022, then drastically worse following COVID-infection in the weeks after being vaccinated, with fever, pain, and headache for 6 weeks. Admitted to pediatric department April 2022, blood tests and abdominal scan normal. Symptoms deteriorating, lost all muscle power, unable to walk. MR cerebrum normal. No school for more than a year, being homeschooled. Referred to psychiatric department due to suspected autism, awaiting diagnosis. Symptoms improved slightly the last months. Contacted private practice specialist hereafter and was diagnosed with Post viral fatigue syndrome.	Yes (fatigue, nausea, headache)	Yes (fatigue, nausea, headache)	DG442 Tension-type headache (+ DZ038 Observation for other suspected diseases and conditions), DF849 Pervasive developmental disorder, unspecified	DG933 Post viral fatigue syndrome	Immediate
7	Received 1st COVID-19 vaccine without adverse reactions. Two months after 2nd dose, abdominal pain, fever, headache, and vomiting, lasting for two months on/off. Developed edema around the eye, proteinuria, hematuria. Hospitalized, with negative strep A test despite signs of tonsillitis. Suspected post-infectious glomerulonephritis.	None	Yes (abdominal pain, fever, headache, vomiting, proteinuria and hematuria)	DN009 Acute nephritic syndrome, unspecified	-	After two months
8	Headache and nausea a few days after 1st dose. After 2nd dose increased headache, vision disturbances, oral blisters, stomachache, and lymphadenitis. Admitted to hospital, abdominal scans, and blood tests normal. Contacted private practice physician hereafter and was diagnosed with Post viral fatigue syndrome.	Yes (headache and nausea)	Yes (increased headache, vision disturbances, oral blisters, stomachache, and lymphadenitis)	DR104 Other and unspecified abdominal pain	DG933 Post viral fatigue syndrome	A few days after dose 1, increasing after dose 2
9	COVID-19 infection one month after being vaccinated. Six months after the vaccine, debuting with increased stomachache and nausea. For more than a year only attending school for one to two hours daily due to fatigue and brain-fog. Hospitalized, abdominal scans normal.	None	Yes (late-occurring stomachache and nausea)	DR104 Other and unspecified abdominal pain	-	Several months
10	COVID-19 infection one month after being vaccinated. Six months after, debut of increasingly worse stomachache, tired. Symptoms persisting for six months and followed by development of fever, nausea, and oral candidiasis two times. Approximately one year after 1st vaccine experiencing vision impairment and headache. Hospitalized. MR cerebrum	None	Yes (stomachache, tired, late-occurring vision impairment, headache, oral candida)	DK590 Constipation	Currently being investigated for Multiple sclerosis (suspected but not registered as code)	Several months

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	with 2 plaques, awaiting new MR and lumbar puncture, suspected Multiple Sclerosis.					
11	Fever, nausea and vomiting one week after 1st vaccine. Hereafter suddenly development of a big black/red marks on leg, with no prior trauma. Admitted to hospital, blood tests showed thrombocytopenia.	Yes (fever, nausea and vomiting, black/red marks on leg)	NA	DD693 Idiopathic thrombocytopenic purpura	-	One week
12	Pain in the neck slowly developing over four months after being vaccinated. Slowly spreading to shoulder and back, movements impaired. Admitted to hospital, MR scan with benign tumor in cervical columnar.	None	Yes (pain in the neck)	DM610 Myositis ossificans traumatica	-	Slowly developing over months
13	Behavior changes started a week after 1st vaccine, with mental regression and infant-like behavior. Headache after 2nd vaccine, and on day two suddenly a generalized seizure. Hereafter left side paralysis, delusions, and continued seizures. Admitted to hospital, suspected autoimmune encephalitis.	Yes (mental regression)	Yes (headache, paralysis, delusions, seizures)	DG049 Encephalitis, myelitis, and encephalomyelitis, unspecified, DR252 Cramp and spasm	-	One week
14	Received 1st COVID-19 vaccine without adverse reactions. Two months after 2nd vaccine, oral blisters, bruises on legs without prior trauma. Fever. Admitted to hospital, suspected Kawasaki and/or Adenovirus infection. Treated with intravenous immunoglobulin with no effect. Developed acute uveitis bilateral, continued bruising. Now suspected Mb Behçet.	None	Yes (fever, oral blisters, bruises on legs, uveitis)	DH441 Other endophthalmitis	Currently being investigated for Behçet disease (suspected but not registered as code)	Two months after
15	No immediate adverse reaction to being vaccinated, but over the next three months a 10 kg weight loss, tired, fatigue. Admitted to pediatric department due to high blood sugar. Quickly received a diagnosis of Diabetes Mellitus type 1. No familiar dispositions.	None	Yes (late-occurring weight loss, tired, fatigue)	DE10 Type 1 diabetes mellitus	-	Slowly developing over months
16	Right-sided facial paralysis three days after 1st vaccine, the next day total right sided hemiparalysis. Hospitalized, MR cerebrum showed a 3 mm plaque, with a follow-up scan showing an expansion to 9 mm within 14 days. Symptoms mimicking multiple sclerosis.	Yes (right-sided facial paralysis, hemiparalysis)	Not vaccinated	DG379 Demyelinating disease of central nervous system, unspecified, DR252 Cramp and spasm	-	Three days
17	Increasingly tired after 1st vaccination. Long recovery time after simple viral infections. Six months after being vaccinated, subfebrile, diffuse joint-and muscle pain, fatigue. Admitted to pediatric department, MR cerebrum and blood tests normal. Offered socio-pediatric admission but instead contacted private practicing physician and was diagnosed with post-viral fatigue syndrome. Slow improvement but still low threshold for activity and concentration. High absence from school. Contacted private practice specialist hereafter and was diagnosed with Post viral fatigue syndrome.	Yes (tired)	Yes (late-occurring fever, diffuse joint-and muscle pain, fatigue)	DZ038 Observation for other suspected diseases and conditions, DR519 Headache, unspecified	DG933 Post viral fatigue syndrome	Six months
18	Possible COVID-19-infected in March 2020, not tested but several weeks of fatigue, brain fog and concentrations problems. Severely worsened after both 1st and 2nd vaccine at the end of 2021, and to date still symptoms. Admitted to both psychiatric and neurological departments, were diagnosed with depression and post viral fatigue syndrome. Several weeks of school absence during the last two years.	Yes (fatigue, brain fog)	Yes (fatigue, brain fog)	DF339 Depression, unspecified, DG933 Post viral fatigue syndrome	-	Immediate
19	Flu-like symptoms after 1st vaccine. Headache and fever lasting for several weeks. Admitted to hospital, diagnosis of conjunctivitis and sinusitis. For months after debut of symptoms experiencing both near-syncope and syncope. Diagnosed with complex regional pain syndrome by private practice physician.	Yes (headache, fever, conjunctivitis, sinusitis)	Yes (headache, fever, near-syncope, syncope)	DJ32 Chronic sinusitis	DM890 Complex regional pain syndrome	Days
20	Fever and nausea after both vaccines. On day two after 2nd injection a sudden severe pain in left arm (injection site) and leg, lasting for 24 hours. No GP or hospital contacts.	Yes (nausea, fever)	Yes (nausea, fever)	-	-	Days
21	Fever after 1st vaccine. In the months after 2nd vaccine black/red spots on leg without trauma, as well as palpable discolored lumps on shins six months after being vaccinated. Admitted to hospital with 3 arterial blood clots in lower leg, estimated to have been present for two to six months. No cardiac disease, no thrombophilia.	Yes (fever)	Yes (black/red spots on leg, discolored lumps on shins)	DI743 Embolism and thrombosis of arteries of lower extremities	-	Months

*Codes obtained at a private specialist clinic – not routinely recorded in the Danish registers

From vaccination to debut of symptoms, the time span was broad, ranging from immediate onset of symptoms within hours or days in just over half of participants (11 children, 52%), and up to several months following immunization in the remaining ten children. Eleven children (52%) reported their adverse event following the first dose, ten following the second dose (Table 2). Eight (38%) reported worsening of a post-dose-1-event after the second dose.

Five children (24%, participants 1, 2, 4, 5 and 6) had a positive COVID-19 PCR test prior to vaccination. Participants 9 and 10 (10%) had a positive COVID-19 PCR test

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after vaccination but prior to onset of symptoms. A total of 11 children (52%) had a positive COVID-19 test months after their vaccination and first occurrence of symptoms, whereas three (14%) never tested positive for COVID-19.

Most children (17, 81%) had at least one visit within the hospital system and thus received one or more ICD-10 diagnoses. Nine (43%) had symptoms compatible with autoimmune illnesses: demyelinating diseases (participant 10, 14 and 16), encephalitis (participant 13), endophthalmitis (participant 14), type 1 diabetes (participant 15), arterial thrombosis (participant 21), glomerulonephritis (participant 7) and idiopathic thrombocytopenia purpura (ITP) (participant 11).

The three children who at the time of the interviews were being investigated for Behcet disease (participant 14) and Multiple Sclerosis (participant 10 and 16) were not ICD-10 coded as such. Six children (29%, participants 1, 3, 4, 6, 17 and 19) reported symptoms of ongoing/chronic infections dominated by long-lasting fever, and a total of five children (24%, participants 2, 6, 8, 17 and 18) received a diagnosis of post-viral fatigue syndrome, a condition that may develop into myalgic encephalomyelitis/chronic fatigue syndrome (ME/CSF).[18]

In a post hoc supplementary analysis, we searched for published literature related to the described diseases. The results can be found in Supplementary Table 1. Seven of the diseases described by our participants and listed in Supplementary Table 1 had been registered during mRNA COVID-19 vaccine phase 3 trial in children and/or adults (demyelinating disease of CNS, type 1 diabetes, encephalitis, thrombocytopenia, chronic sinusitis, and depression).

Six conditions have been reported in post-surveillance pharmacovigilance studies (nephritic syndrome, demyelinating diseases, encephalitis, arterial embolisms, ITP, and thrombocytopenia), but without a statistically significant association. Ten conditions (including the ones described above as reported through pharmacovigilance) have been reported as single case reports or case studies. Depression has been reported in a cohort study, post-viral fatigue syndrome in an exploratory study. No published literature on pervasive development disorder was found.

Headache, fever, nausea and abdominal symptoms that were reported by seventeen participants are all common immediate adverse reactions to vaccines and were also frequently reported during the phase 3 trials.

Participants 7, 8, 13, 14, 16 and 17 all reported their newly-onset disease to the Danish Medicines Agency, and in addition, participants 13 and 16 also reported the disease to the Danish Patient Compensation. Both cases were evaluated as not being related to the vaccine.

5. Discussion

This original investigation presents a selection of potential adverse events as experienced by Danish children following COVID-19 vaccination. Most children had diseases within the autoimmune spectrum but there was no uniformity in ICD-10 diagnoses, except for the five children with a diagnosis of post-viral fatigue syndrome. Also, the time interval between vaccination and symptoms debut varied and in 24%, there was a simultaneous positive COVID-19 PCR test.

Study Limitations

This study has important limitations.

First, we used self-reported data, which can introduce information bias. This can be recall bias, where the accuracy usually deteriorates with time, and our interviews were conducted years after the time of vaccination. Selective recall is also a plausible bias, as some events are more easily remembered than others, and looking backwards might lead to the creation of causality between vaccination and the given event.[19]

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Second, the wording of interview questions alters responses, and the answers are information that the one being interviewed perceives as sufficient but may lack information that could have been useful for the interviewer.

Third, seven children had COVID-19 vaccines and infection simultaneously, and it is important to note that many of the symptoms of both acute and long COVID-19 infection are similar to the post-vaccination symptoms,[20] hence some health effects believed to be associated with vaccination may also have been associated with infection alone, both infection and vaccination, neither or both.

Vaccination and autoimmunity

While there was no clear pattern in the reported potential adverse events, a large proportion had autoimmune components. The association between vaccines and autoimmune disease is controversial.[21,22] Post-vaccination autoimmune diseases have been described in the literature for vaccines against Hepatitis B, and measles, mumps and rubella (MMR), but there exist no general criteria for diagnosing vaccine-related autoimmune disease.[21] A recent preprint investigated what was coined chronic post-vaccination syndrome (PVS) after COVID-19 vaccination in 241 adults. Many of the symptoms could be elicited by autoimmune diseases.[23] Another recent preprint describes how 131 of 191 participants suffering from long-lasting sequelae of mRNA COVID-19 vaccination fit the ME/CSF diagnosis.[24]

A relationship between viral infections and autoimmunity has also been recognized, with many different trigger mechanisms, including a proinflammatory cytokine release by the innate immune system resulting in prolonged proinflammatory responses.[22,25] Hence, viral infections such as Cytomegalovirus, Epstein-Barr Virus and Rubella have been associated with autoimmune diseases such as diabetes mellitus type 1 and multiple sclerosis.[25] Recently it was shown that COVID-19 infection could contribute to the emergence of autoimmunity in predisposed individuals,[26] and that patients with COVID-19 had increased levels of interleukin (IL) 1 and IL-6 as well as tumor necrosis factor (TNF)-?.[27] These cytokines may play a role in the development of autoimmune diseases in genetically predisposed individuals.[28] Proinflammatory cytokines including IL-6 were also shown to be increased following mRNA COVID-19 vaccination, indicating that an association between vaccination and autoimmune disease is plausible.[29,30]

Vaccination and other infections

Vaccines may have non-specific/heterologous effects, i.e. an ability to not only protect against the target disease, but also affect the risk of non-targeted infections, either beneficially or negatively, depending on vaccine type and the sex of the vaccinee.[31] In the present study, six children presented with long-lasting fever, but only one had a relevant ICD-10 diagnosis (chronic sinusitis).

Consistency with phase 3 trial observations and post-marketing findings

Headache, fever, nausea and abdominal symptoms reported by 17/21 participants were already described as solicited adverse reactions during COVID-19 mRNA vaccine phase 3 trials. In the current study, these symptoms were described as long-lasting, but few participants were provided with an ICD-10 diagnosis (Table 2). A recent paper pointed out that many of the reported long-lasting adverse events after COVID-19 vaccination presented as a prolonged version of normal vaccination reactions, and this may hamper their detection, as the duration of these well-known adverse drug reactions are not easily captured in the pharmacovigilance systems and would likely be interpreted as transient adverse reactions.[32]

SAEs reported during the phase 3 trials in children aged 0-17 years included depression, pyelonephritis, idiopathic epilepsy (generalized), and type 1 diabetes,

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diseases which were also reported in this study. The descriptions of these events are not available in the clinical trials' published main texts but can be found in either supplementary material or in the FDA/EMA reports.[33,34,35]

Overall, there was little evidence of association between vaccination and the symptoms described by our participants in the existing literature, as most of the published studies were case-based or showed non-significant associations (Supplementary Table 1).

Identifying rare diseases through register-based studies

The main aim of the study was to identify experienced symptoms following COVID-19 vaccination and their timing, to assess whether associations could be studied by using register data.

We found that some children were yet to receive a final or confirmed diagnosis due to the complexity of the disease pattern. Hence, only minor symptoms, such as headache or stomachache, were registered for these children although they are currently suspected of and assessed for serious diagnoses such as Behcet s disease and Multiple Sclerosis. Thus, many register-based studies aiming to investigate associations between COVID-19 vaccines and these ICD-10 codes, often limiting themselves to diagnoses given within a certain time frame of vaccination,[36] would not include these events. This highlights the importance of using different time windows in the study of potential vaccine-related adverse events.

6. Conclusion

In this original investigation, 21 cases with new-onset disease following COVID-19 vaccination were presented. A variety of diseases were described by the participants, many with an autoimmune or infectious aspect. The present study cannot establish any causal relations between COVID-19 vaccines and the observed diseases. Future register-based studies should consider combining groups of ICD-10 codes and aim to include diagnoses from specialists as well as consider different time windows following vaccination.

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Ethics:

All participants provided oral and written consent to the publishing of their personal data.

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Data accuracy and data sharing:

All authors affirm that the manuscript is an accurate and transparent presentation

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of the studies being reported, and that all relevant data has been published.

Author contributions:

The study was conceptualized by CSB, SH, SMT and AP. SH conducted the interviews and wrote the first draft of the paper. SH and CBS did the literature searches. All authors approved the final version.

References

1. WHO. WHO Coronavirus (COVID-19) Dashboard With Vaccination Data. 2023. Accessed July 26, 2023. https://covid19.who.int/
2. Our World in Data. COVID-19 vaccine doses administered by manufacturer, European Union. 2023. https://ourworldindata.org/grapher/covid-vaccine-doses-by-manufacturer
3. Hoffmann SS, Nielsen S, Thysen SM, Duriseti R, Benn CS. Overall Health Effects of mRNA COVID-19 Vaccines in Children and Adolescents A Systematic Review and Meta-Analysis. Published online January 18, 2024:2023.12.07.23298573. doi:10.1101/2023.12.07.23298573
4. Frenck RW, Klein NP, Kitchin N, et al. Safety, Immunogenicity, and Efficacy of the BNT162b2 Covid-19 Vaccine in Adolescents. N Engl J Med. 2021;385(3):239-250. doi:10.1056/nejmoa2107456
5. Walter EB, Talaat KR, Sabharwal C, et al. Evaluation of the BNT162b2 Covid-19 Vaccine in Children 5 to 11 Years of Age. N Engl J Med. 2022;386(1):35-46. doi:10.1056/NEJMOA2116298
6. Muñoz FM, Sher LD, Sabharwal C, et al. Evaluation of BNT162b2 Covid-19 Vaccine in Children Younger than 5 Years of Age. N Engl J Med. 2023;388(7):621-634. doi:10.1056/NEJMOA2211031
7. Ali K, Berman G, Zhou H, et al. Evaluation of mRNA-1273 SARS-CoV-2 Vaccine in Adolescents. N Engl J Med. 2021;385(24):2241-2251. doi:10.1056/nejmoa2109522
8. Creech CB, Anderson E, Berthaud V, et al. Evaluation of mRNA-1273 Covid-19 Vaccine in Children 6 to 11 Years of Age. N Engl J Med. 2022;386(21):2011-2023. doi:10.1056/NEJMOA2203315
9. Anderson EJ, Creech CB, Berthaud V, et al. Evaluation of mRNA-1273 Vaccine in Children 6 Months to 5 Years of Age. N Engl J Med. 2022;387(18):1673-1687. doi:10.1056/nejmoa2209367
10. Chua GT, Kwan MYW, Chui CSL, et al. Epidemiology of Acute Myocarditis/Pericarditis in Hong Kong Adolescents Following Comirnaty Vaccination. Clin Infect Dis. 2022;75(4):673-681. doi:10.1093/cid/ciab989
11. Sardella M, Belcher G. Pharmacovigilance of medicines for rare and ultrarare diseases. Ther Adv Drug Saf. 2018;9(11):631. doi:10.1177/2042098618792502
12. Onakpoya IJ. Rare adverse events in clinical trials: Understanding the rule of three. BMJ Evid-Based Med. 2018;23(1):6. doi:10.1136/EBMED-2017-110885
13. Thygesen LC, Daasnes C, Thaulow I, Brønnum-Hansen H. Introduction to Danish (nationwide) registers on health and social issues: structure, access, legislation, and archiving. Scand J Public Health. 2011;39(7 Suppl):12-16. doi:10.1177/1403494811399956
14. Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. Clin Epidemiol. 2015;7:449-490. doi:10.2147/CLEP.S91125

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15. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. Scand J Public Health. 2011;39(7 Suppl):30-33. doi:10.1177/1403494811401482

16. Henriksen DP, Rasmussen L, Hansen MR, Hallas J, Pottegård A. Comparison of the Five Danish Regions Regarding Demographic Characteristics, Healthcare Utilization, and Medication Use--A Descriptive Cross-Sectional Study. PloS One. 2015;10(10):e0140197. doi:10.1371/journal.pone.0140197

17. Statens Serum Institut. Childhood vaccination programme. Childhood vaccination programme. Accessed August 13, 2023. https://en.ssi.dk/vaccination/the-danish-childhood-vaccination-programme

18. O'Boyle S, Nacul L, Nacul FE, et al. A Natural History of Disease Framework for Improving the Prevention, Management, and Research on Post-viral Fatigue Syndrome and Other Forms of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Front Med. 2022;8:688159. doi:10.3389/fmed.2021.688159

19. Althubaiti A. Information bias in health research: definition, pitfalls, and adjustment methods. J Multidiscip Healthc. 2016;9:211-217. doi:10.2147/JMDH.S104807

20. Scholkmann F, May CA. COVID-19, post-acute COVID-19 syndrome (PACS, "long COVID") and post-COVID-19 vaccination syndrome (PCVS, "post-COVIDvac-syndrome"): Similarities and differences. Pathol - Res Pract. 2023;246:154497. doi:10.1016/j.prp.2023.154497

21. Olivieri B, Betterle C, Zanoni G. Vaccinations and Autoimmune Diseases. Vaccines 2021 Vol 9 Page 815. 2021;9(8):815. doi:10.3390/VACCINES9080815

22. Chatterjee S, Bhattacharya M, Saxena S, Lee SS, Chakraborty C. Autoantibodies in COVID-19 and Other Viral Diseases: Molecular, Cellular, and Clinical Perspectives. Rev Med Virol. 2024;34(5):e2583. doi:10.1002/rmv.2583

23. Krumholz HM, Wu Y, Sawano M, et al. Post-Vaccination Syndrome: A Descriptive Analysis of Reported Symptoms and Patient Experiences After Covid-19 Immunization. Published online November 10, 2023:2023.11.09.23298266. doi:10.1101/2023.11.09.23298266

24. Mundorf AK, Semmler A, Heidecke H, et al. Clinical and Diagnostic Features of Post-Acute COVID-19 Vaccination Syndrome (PACVS). Vaccines. 2024;12(7):790. doi:10.3390/vaccines12070790

25. Sundaresan B, Shirafkan F, Ripperger K, Rattay K. The Role of Viral Infections in the Onset of Autoimmune Diseases. Viruses. 2023;15(3):782. doi:10.3390/v15030782

26. Ehrenfeld M, Tincani A, Andreoli L, et al. Covid-19 and autoimmunity. Autoimmun Rev. 2020;19(8):102597. doi:10.1016/J.AUTREV.2020.102597

27. Qin C, Zhou L, Hu Z, et al. Dysregulation of Immune Response in Patients With Coronavirus 2019 (COVID-19) in Wuhan, China. Clin Infect Dis. 2020;71(15):762-768. doi:10.1093/cid/ciaa248

28. Masters SL, Simon A, Aksentijevich I, Kastner DL. Horror autoinflammaticus: the molecular pathophysiology of autoinflammatory disease (*). Annu Rev Immunol. 2009;27:621-668. doi:10.1146/annurev.immunol.25.022106.141627

29. Noé A, Dang TD, Axelrad C, et al. BNT162b2 COVID-19 vaccination in children alters cytokine responses to heterologous pathogens and Toll-like receptor agonists. Front Immunol. 2023;14:1242380. doi:10.3389/FIMMU.2023.1242380/BIBTEX

30. Semmler A, Mundorf AK, Kuechler AS, et al. Chronic Fatigue and Dysautonomia following COVID-19 Vaccination Is Distinguished from Normal Vaccination Response by Altered Blood Markers. Vaccines. 2023;11(11):1642. doi:10.3390/vaccines11111642

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ISSN: 3067-6614 (Online)

31. Benn CS, Fisker AB, Rieckmann A, Sørup S, Aaby P. Vaccinology: time to change the paradigm? Lancet Infect Dis. 2020;20(10):e274-e283. doi:10.1016/S1473-3099(19)30742-X

32. Platschek B, Boege F. The Post-Acute COVID-19-Vaccination Syndrome in the Light of Pharmacovigilance. Vaccines. 2024;12(12):1378. doi:10.3390/vaccines12121378

33. EMA. Assessment report Procedure No. EMEA/H/C/005735/X/0077. Published online 2021. https://www.ema.europa.eu/en/documents/variation-report/comirnaty-h-c-5735-x-0077-epar-assessment-report-extension_en.pdf

34. EMA. Assessment report Procedure No. EMEA/H/C/005735/X/0138. Published online 2022. Accessed August 3, 2023. https://www.ema.europa.eu/en/documents/variation-report/comirnaty-h-c-005735-x-0138-epar-assessment-report-extension_en.pdf

35. FDA. Vaccines and Related Biological Products Advisory Committee June 14-15, 2022 Meeting Presentation. Published online 2022. https://www.fda.gov/media/159157/download

36. Husby A, Hansen JV, Fosbøl E, et al. SARS-CoV-2 vaccination and myocarditis or myopericarditis: population based cohort study. BMJ. 2021;375:e068665. doi:10.1136/bmj-2021-068665

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